Combined Chemoradiotherapy for Early Glottic Cancer in Clinical Practice in Japan: Analysis of 10 Institutions

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Abstract. *Aim: To conduct a retrospective analysis regarding treatment strategies for early glottic cancer (GC) at ten institutions. Patients and Methods: A questionnaire-based survey was used to obtain personal and medical information on patients who started radiation therapy for T1 or T2 GC between January 2000 and December 2005. Results: A total of 279 patients were registered for the survey, of whom 124 patients were classified as T1a, with 65 patients as T1b and 87 patients as T2. The rates of chemoradiotherapy for T1a, T1b and T2 were 24%, 23% and 60%, respectively. A comparison of results for academic and non-academic hospitals showed statistically different rates of combination therapy for T1a (6.9% vs. 39.3%, respectively; p<0.001) and T1b (11.4% vs. 36.6%, respectively; p<0.05) but not for T2 (70.0% vs. 54.4%, respectively; p=0.158). Conclusion: In clinical practice, combined chemoradiotherapy was performed for early GC at most institutions in Tokai District, Japan.*

The larynx is composed of three parts: the supraglottis, glottis and subglottis. Glottic cancer (GC), the most common laryngeal cancer, is usually detected early due to the symptomatic occurrence of a hoarse voice.

According to recently published guidelines for head and neck cancer treatment (1, 2), all patients with T1-T2 laryngeal cancer should be treated, at least initially, with the intent of larynx preservation. The recommended strategies for early GC are radiation therapy (RT), transoral laser therapy and partial laryngectomy (1, 2). Chemoradiotherapy is not included in the recommendations for early GC. Currently, RT alone is the initial treatment of choice at most institutions, with surgery being reserved as a salvage option for local failure.

In Japan, however, combined chemoradiotherapy is administered for early GC in clinical practice. The details of chemoradiotherapy for early GC are unknown, and no multicenter survey has been conducted as a comprehensive study of the patterns of care in clinical and research treatment. In the present study, the clinical practice in terms of treatment for early GC in Japan was investigated. While a nationwide survey was not conducted, results of a survey conducted at ten institutions in Tokai District are presented.

Patients and Methods

The Tokai Study group for Therapeutic Radiology and Oncology (TOSTRO) conducted a questionnaire-based concerning radiation therapy for early GC in 2008. The questionnaire included questions concerning the stage of cancer (T1a, T1b or T2 according to the sixth UICC, (3) International Union Against Cancer classification system, 2002), age, sex, performance status, histology, radiation dose, fraction size and method, total radiation dose and combination chemotherapy among patients for whom RT was started between January 2000 and December 2005. The data from ten institutions were recorded. Statistical significance was tested using the Chi-square test. The results were considered statistically significant at the level of $p<0.05$. This study was approved by the Ethics Board of each participating hospital.

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Table I. *Patient characteristics*.

	n	%
Total patients	279	100
Age, years, median (range)	67 (43-92)	
Male/Female	269/10	96/4
Performance status (ECOG)		
0-1	262	94
2	5	2
Unknown	12	4
Histology		
Squamous cell carcinoma	279	100
Stage (UICC)		
T1a	124	44
T1b	65	23
T1 unknown	3	1
T2	87	31

UICC: International Union Against Cancer; ECOG: Eastern Cooperative Oncology Group.

Table II. *Fractionation method and radiation dose*.

	n	%
Conventional fractionation (CF)	238	85
Median dose (dose range)	69.8 Gy (6-82 Gy)	
Hyperfractionation (HF)	24	9
Median dose (dose range)	76.8 Gy (67.6-76.8 Gy)	
Accelerated hyperfractionation (AHF)	5	2
Median dose (dose range)	72 Gy (60-72 Gy)	
CF+HF	6	2
Median dose (dose range)	67.1 Gy (54.4-76.8 Gy)	
CF+AHF	6	2
Median dose (dose range)	68.5 Gy (56.5-71 Gy)	

Results

Patient characteristics. Table I shows the characteristics of the 279 patients surveyed, 269 (96%) of whom were male and the median age was 67 years. For all the patients, the histological diagnosis of GC was squamous cell carcinoma. For 124 patients, the tumors were classified as T1a, while 65 patients had T1b tumors, and in three cases of T1 tumors, the subtype was unknown.

Treatment details. Radiotherapy: The various fractionation methods and radiation doses that had been used during the treatment of the 279 patients are summarized in Table II. All the patients had been treated with parallel-opposed fields at 4 MV or 6 MV. Wedge filters of 15 or 30 degrees had been used to optimize the dose distribution to achieve a homogeneity of ±5%. No prophylactic neck irradiation was performed in any of the cases.

Chemotherapy: The rate of combined chemoradiotherapy at each stage and the various chemotherapy drugs and regimens that had been used are listed in Table III. Out of 98 patients who had undergone combination therapy, 82% had been treated with concurrent therapy, 13% with neoadjuvant therapy, 4% with alternative therapy and 1% with adjuvant therapy. The most commonly used chemotherapeutic regimen had been a high dose of CDDP/5-FU, followed by UFT (an oral antidrug) and weekly carboplatin. When the institutes were divided into academic hospitals and non-academic hospitals according to the institutional stratification of patterns of care study (PCS) in Japan (4), the combination therapy rates were statistically different between the two types of hospital for T1a (6.9% *vs*. 39.3%, respectively; $p<0.001$) and T1b (11.4% *vs*. 36.6%, respectively; $p<0.05$), but not for T2 (70.0% *vs*. 54.4%, respectively; $p=0.158$) (Table IV).

Discussion

Chemoradiotherapy for early GC is not mentioned in well-known textbooks of radiation oncology (5-6). Recent studies have shown these to be an improvement in local control for patients with T1 and T2 GC when total radiation is delivered following a high-dose fractionation (7-8) or hyperfractionation schedule (9-11) over a shorter overall treatment time. In the current study, 15% of the 279 patients were treated on hyperfractionation schedules. At the ten institutions surveyed in the current study, however, combined chemoradiotherapy with various fractionation schedules had been carried out for early GC in clinical practice. The rates of combination therapy for T1a, T1b and T2 were 24%, 23% and 60%, respectively (Table III). Moreover, the rates of combination therapy for T1a and T1b were statistically different between the two hospital types (Table IV).

Combination therapy may be used for several reasons. First by, most otolaryngologists believe that local control by radiation alone is insufficient (12). Radiation alone has been reported to be about 80-90% effective (5-7, 13-15) for local control of T1 GC and 65-80% (5, 6, 14, 16) effective for T2 GC. According to some reports, the local control for bulky T1 is about 70% (17, 18).

Second by, chemoradiotherapy has been suggested for laryngeal preservation in advanced cases. In a phase III study of patients with local advanced laryngeal cancer (19), radiotherapy with concurrent administration of cisplatin was found to be superior to induction chemotherapy followed by radiotherapy or radiotherapy alone for laryngeal preservation and locoregional control. The rate of laryngeal preservation was 84% among patients receiving radiotherapy with concurrent cisplatin. In fact, many of the chemoradiation regimens listed in Table III are used for advanced head and neck cancer.

Table III. *Combination therapy rate and regimens used.*

	Combined therapy (%)	Radiation alone (%)	Total
T1a	30 (24)	94 (76)	124
T1b	15 (23)	50 (77)	65
T1 unknown	1 (33)	2 (66)	3
T2	52 (60)	35 (40)	87
Regimen		n (%)	
Low-dose CDDP (daily)		8 (8)	
Low-dose CDDP/5-FU (daily)		5 (5)	
High-dose CDDP/5-FU		32 (33)	
Carboplatin (daily)		1 (1)	
Carboplatin (weekly)		2 0 (20)	
CDDP/5-FU/DTX		5 (5)	
DTX		3 (3)	
UFT (oral antidrug)		22 (22)	
S-1 (oral antidrug)		2 (2)	

CDDP: Cisplatin, 5-FU: fluorouracil, DTX: docetaxel, UFT: tegafur + uracil, S-1: tegafur + gimeracil + oteracil.

Finally, several reports have indicated that chemoradiation for T2GC is promising and yields local control rates higher than those for RT alone in Japan (20-24). Chemoradiation for bulky T1 and T2 GC is used with the intent to improve local control in clinical practice in Japan.

In non-academic hospitals, the rate of combination therapy for T1a and T1b was statistically higher than in the university hospitals. Otolaryngologists may not be satisfied with local control by radiation alone, and non-academic hospitals do not have enough surgical specialists to perform salvage surgery for local failure, so patients with a local recurrence must sometimes be sent to another hospital for surgery. Consequently, chemoradiotherapy may be used for early GC to reduce local failure by all possible means.

In a recent paper, Chera *et al*. have recommended concurrent systemic platinum-based chemotherapy, preferably weekly cisplatin (30 mg/m^2), for patients with T2b tumors (25). Because chemoradiotherapy for early GC will probably become more common throughout the world, a large-scale trial of chemoradiotherapy for T2 GC should be conducted in Japan. First of all, however, consideration must be made regarding the choice of anticancer drugs and the optimal dosing schedule for T2 GC.

In conclusion, combined chemoradiotherapy was administered for early GC in clinical practice at most of the participating institutions. At the non-academic hospitals, the rate of combination therapy was statistically higher for T1a and T1b GC than that at the academic hospitals.

Table IV. *The rate of chemoradiotherapy at university and non-university hospitals.*

	University hospitals (n=3)	Non-academic hospitals (n=7)	*p*-Value
T1a	4/58 (6.9%)	26/66 (39.3%)	<0.001
T1b	4/35 (11.4%)	11/30 (36.6%)	<0.05
T2	21/30 (70.0%)	31/57 (54.4%)	0.158

Three cases with unknown T1 subtypes were excluded.

Conflict of Interest

There is no conflict of interest regarding this study.

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